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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 04/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/839,658	BRADLEY ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,17,67 and 68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,17,67 and 68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 10, 2004 has been entered.

2. Claims 1-17, 67 and 68 were previously pending. Applicants amended claim 1 and cancelled claims 15 and 16. Claims 1-14, 17, 67 and 68 are pending and will be examined.

3. Applicants' amendments and claim cancellations overcame the following rejections: rejection of claims 15 and 16 under 35 U.S.C. 112, second paragraph; rejection of claims 1, 2, 6, 7, 12-17, 67 and 68 under 35 U.S.C. 102(b) as anticipated by Huang et al.; rejection of claims 1-8, 12, 14-17, 67 and 68 under 35 U.S.C. 102(b) as anticipated by Cronin et al.; rejection of claim 9 under 35 U.S.C. 103(a) over by Cronin et al. and Waggoner et al.; rejection of claim 10 under 35 U.S.C. 103(a) over by Cronin et al. and Anderson; rejection of claim 11 under 35 U.S.C. 103(a) over by Cronin et al. and Ordahl et al.; rejection of claim 13 under 35 U.S.C. 103(a) over by Cronin et al. and Anderson et al.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 depends from cancelled claims 15 and 16.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-8, 12, 13, 17, 67 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. (Human Mutation, vol. 7, pp. 244-255, 1996; cited in the previous office action), Solinas-Toldo et al. (Genes Chrom. Cancer, vol. 20, pp. 399-407, 1997), in view of Dorin et al. (Trends in Biotechn., vol. 9, pp. 48-52, 1991) and Zielenski et al. (Nature Genetics, vol. 22, pp. 128-129, June 1999).

Regarding claim 1, Cronin et al. teach detection of cystic fibrosis mutations by hybridization of target nucleic acids to an array of plurality of immobilized probes by the method comprising:

(a) providing the plurality of nucleic acid probes comprising a plurality of immobilized nucleic acid segments in an array with each probe at a known location (Cronin et al. teach two types of arrays with plurality of probes: one had probes which allowed identification of differences from the wild type sequences in exon 11, the second array contained 1480 probes for detection of deletions, insertions and base substitutions (Abstract; page 245, 246).);

(b) contacting the immobilized probes with a sample of target nucleic acid comprising fragments of genomic nucleic acid labeled with a detectable moiety, wherein each labeled fragment consists of a length smaller than about 200 bases, and the contacting is under conditions allowing hybridization of the target nucleic acid to the probe nucleic acid (Cronin et al. teach preparation of genomic DNA target used in the hybridization experiments by amplification, labeling with

fluorescein by amplification with fluorescein-labeled nucleotides, then fragmentation of the amplification products with uracil-N-glycosylase. The fragmented PCR products were 20-60 bp long (page 247, second paragraph). The target DNA fragments were contacted with the immobilized probes under conditions which permitted hybridization of the target to the probes (page 247, third paragraph; Fig. 2).); and

(c) observing an amount and location of labeled genomic nucleic acid hybridized to each immobilized probe, to detect regions of amplification, deletion and unique sequences in the sample, thereby generating a molecular profile of the sample genomic nucleic acid (Cronin et al. teach observation of hybridization events using a confocal epifluorescent microscope and detection of mutations (= unique sequences) (page 247, paragraphs 4-6; page 248, first paragraph; Fig. 2; Fig. 3; Tables 1 and 2).

Regarding claims 2-6, Cronin et al. teach labeled fragments in the range of 20-60 bp long, which are no more than about 150, or about 100, or about 50, or about 30 bp, and in the range between about 30 to about 150 bases.

Regarding claim 7, Cronin et al. teach preparation of genomic DNA target used in the hybridization experiments by amplification, labeling with fluorescein by amplification with fluorescein-labeled nucleotides, then fragmentation of the amplification products with uracil-N-glycosylase.

Regarding claim 8, Cronin et al. teach preparation of genomic DNA target used in the hybridization experiments by amplification, labeling with fluorescein by amplification with fluorescein-labeled nucleotides (= detectably labeled base pairs), then fragmentation of the amplification products with uracil-N-glycosylase.

Regarding claim 12, Cronin et al. teach stringent hybridization conditions (page 245, second column).

Regarding claims 14, 17, 67 and 68, Cronin et al. teach total genomic samples obtained from human CFTR patients, therefore the samples contained total human genome and all of human chromosomes (page 247, first paragraph).

B) Cronin et al. teach that it is difficult to develop clinical tests for cystic fibrosis, since the CFTR gene spans over 250 kilobases of DNA and contains at least 500 different mutations, including insertions and deletions (page 244, first paragraph). Cronin et al. do not teach probes representing all or a part of chromosome or genome, and probes being members of a genomic library cloned in a vector having a nucleic acid insert greater than about 50 kilobases.

C) Regarding claim 1, Solinas-Toldo et al. teach detection of gains and losses in genomic regions by using whole human genomes, in the form of YACs, Bacs, PACs or cosmids (page 400, second paragraph). Solinas-Toldo et al. teach arraying of vector libraries (PACs), with inserts in the range of 75-130 kb (page 400, last paragraph), onto glass slides, and hybridization of whole genomic DNAs to the arrays (page 401; page 402, first and second paragraph; Fig. 1). The method allowed detection of gene amplifications and deletions (page 404).

Regarding claim 13, Solinas-Toldo et al. teach hybridization of probes and targets at 60° C (page 401, third paragraph).

D) Dorian et al., in a paper written about two years after publication of the CFTR gene sequence, teach identification of over 60 mutations in the CFTR gene, and a necessity to screen for all 60 mutations in cases where one of the parents is positive for an already recognized mutation (page 48, fifth and sixth paragraphs; page 49, first paragraph). Further, Dorian et al. teach that determination of new mutations will be valuable for correlating phenotype with genotype of cystic

fibrosis individuals. For example, the lung disease and pancreatic insufficiency were originally proposed to be in direct correlation with the ΔF508 mutation, but this was shown not be the case, suggesting involvement of other genetic and/or environmental factors (page 49, last two paragraphs; page 50, first paragraph).

E) Zielenski et al. teach identification of a cystic fibrosis related locus on chromosome 19, correlated with a meconium ileus phenotype of cystic fibrosis patients (page 128, first and second paragraphs). Multiple mutations were proposed to exist in this locus (page 129, second paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the vector probes representing whole chromosomes or a whole genome of Solinas-Todo et al. to detect cystic fibrosis mutations of Cronin et al. The motivation to do so, provided by Solinas-Todo et al. would have been that using using arrayed fragments of contiguous genomic DNA allowed for automation of chromosomal amplifications and deletetions, as well as detection of all genomic imbalances relevant to a certain disease (page 406, second paragraph). The motivation to do so, provided Dorian et al., would have been that clinical testing required screening for all possible mutations and detection of new mutations to associate multiple phenotypic manifestations of cystic fibrosis with particular genotypes (page 48, fifth and sixth paragraphs; page 49; page 50, first paragraph). Finally, the motivation to do so, provided by Zielenski et al., would have been that "Larger study populations will be required to refine the chromosome localization of *CFM1* in both humans and mice so that systematic analysis of candidate genes will become feasible. The recently established CF mouse model with a pulmonary phenotype16 may prove to be another useful system to study the modifier gene(s) underlying the variable pulmonary expression observed in the CF population. Identification of modifier genes will permit better understanding of

the clinical heterogeneity of CF and thereby provide insights into prognosis and management." (page 129, last paragraph).

8. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. (Human Mutation, vol. 7, pp. 244-255, 1996; cited in the previous office action), Solinas-Toldo et al. (Genes Chrom. Cancer, vol. 20, pp. 399-407, 1997), in view of Dorin et al. (Trends in Biotechn., vol. 9, pp. 48-52, 1991) and Zielenski et al. (Nature Genetics, vol. 22, pp. 128-129, June 1999), as applied to claim 8 above, and further in view of Waggoner et al. (U. S. Patent No. 5,268,486; cited in the previous office action).

A) Claim 9 is drawn to the label comprising Cy3 or Cy5.

B) Cronin et al. and Solinas-Toldo et al. teach fluorescent labels, but do not teach Cy3 or Cy5.

C) Waggoner et al. teach luminescent cyanine dyes, including Cy3 and Cy 5 (col. 19, formula at the bottom; claim 8; Cy3 has m=1, Cy5 has m=2). the dyes can be used to label nucleic acids (col. 2, lines 58-61; col. 4, lines 29-35).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the cyanine dyes of Waggoner et al. in the method of Cronin et al. and Solinas-Toldo et al. The motivation to do so, provided by Waggoner et al., would have been that cyanine dyes were used for detecting mixtures of components because they had a wide range of excitation and emission wavelengths (col. 4, lines 36-49).

9. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. (Human Mutation, vol. 7, pp. 244-255, 1996; cited in the previous office action), Solinas-Toldo et al. (Genes Chrom. Cancer, vol. 20, pp. 399-407, 1997), in view of Dorin et al. (Trends in Biotechn., vol. 9, pp. 48-52, 1991) and Zielenski et al. (Nature Genetics, vol. 22, pp. 128-129, June 1999), as

applied to claim 1 above, and further in view of Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1981; cited in the previous office action).

A) Claim 10 is drawn to fragmentation of genomic DNA to sizes smaller than 200 bases by DNAse digestion.

B) Neither Cronin et al. nor Solinas-Toldo et al. teach fragmentation of DNA by DNAse digestion.

C) Anderson teaches fragmentation of genomic DNA to sizes below 200 base pairs by digestion with 2.2 ng or more of DNAse I (Figure 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used DNAse I digestion of Anderson to fragment genomic target DNA in the method of Cronin et al. and Solinas-Toldo et al. The motivation to do so, provided by Anderson, would have been that DNAse I digestion was sequence-independent and the sizes distribution obtained could be regulated by regulating the amount of DNAse I in the reaction (page 3019, first two paragraphs).

10. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. (Human Mutation, vol. 7, pp. 244-255, 1996; cited in the previous office action), Solinas-Toldo et al. (Genes Chrom. Cancer, vol. 20, pp. 399-407, 1997), in view of Dorin et al. (Trends in Biotechn., vol. 9, pp. 48-52, 1991) and Zielenski et al. (Nature Genetics, vol. 22, pp. 128-129, June 1999), as applied to claim 1 above, and further in view of Ordahl et al. (Nucl. Acids Res., vol. 3, pp. 2985-2999, 1976; cited in the previous office action) and Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1981; cited in the previous office action).

A) Claim 11 is drawn to fragmentation of genomic DNA to sizes smaller than 200 bases by applying shear forces to fragment genomic DNA followed DNAse digestion.

B) Neither Cronin et al. nor Solinas-Toldo et al. teach fragmentation of genomic DNA to sizes smaller than 200 bases by applying shear forces to fragment genomic DNA followed DNAse digestion.

C) Ordahl et al. teach fragmentation of genomic DNA in preparation for DNA hybridization experiments. Ordahl et al. teach that it is advantageous to use DNA fragments of less than 500 bp in hybridization experiments (page 2985, first paragraph). Ordahl et al. teach that DNA fragmented in French press had an average size of 230 base pairs (Abstract; page 2986; Fig. 4). Ordahl et al. do not teach DNAse I fragmentation after shearing.

D) Anderson teaches fragmentation of genomic DNA to sizes below 200 base pairs by digestion with 2.2 ng or more of DNAse I (Figure 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used shearing of Ordahl et al. and DNAse I digestion of Anderson to fragment genomic target DNA in the method of Cronin et al. and Solinas-Toldo et al. The motivation to do so, provided by Ordahl et al. and Anderson, would have been that it was advantageous to use short DNA fragments in hybridization (Ordahl, p. 2885, first paragraph) and that DNAse I digestion was sequence-independent and the sizes distribution obtained could be regulated by regulating the amount of DNAse I in the reaction (Anderson, page 3019, first two paragraphs).

11. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TS
April 23, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER